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BY EMAIL

11th January 2013

RE: ACD on Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment (ID 518)

Dear [redacted],

Thank you for giving us the opportunity to comment on the ACD for the above appraisal. We are disappointed with the Committee's draft recommendation and hope that the information provided within this response will allow NICE to recommend axitinib as a second-line treatment for patients with advanced/metastatic renal cell carcinoma (mRCC) for whom there is currently no NICE-approved therapy in second-line.

As part of our response we have included clinical evidence to address some of the Committee's key conclusions summarised in the ACD. This is particularly in relation to the external validity of the simulated treatment comparison (STC) results for the prior sunitinib group. In addition, in the context of available clinical evidence and the STC results, we discuss the clinical assumptions underpinning the Evidence Review Group (ERG) exploratory analysis, which the Committee considered as being a more plausible scenario in their draft recommendation. In order to address the ERG's and Committee's concerns about the validity and reliability of the STC due to the lack of CIs or SE around the adjustment factors, we have developed the methodology to estimate these CIs and SE, which is described in Appendix 1.

Finally, the Department of Health have approved the revised patient access scheme (PAS) for axitinib which is included in our response. The updated cost-effectiveness results with the revised PAS are provided in a separate document.

[redacted]

Yours sincerely,

[redacted]

For and on behalf of Pfizer Limited

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Executive Summary

In the preliminary recommendation outlined in the ACD, the NICE committee did not recommend axitinib for the treatment of adults with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine as they concluded that the value of the incremental cost-effectiveness ratios (ICERs) (with the patient access scheme (PAS) applied in the evidence submission), and the uncertainty around the ICERs meant that axitinib still could not be considered a good use of NHS resources for this population. This draft recommendation was based on the conclusion that the results from the STC, and more specifically the post-progression model outputs for the prior sunitinib group, should be interpreted with caution because they lacked clinical plausibility. The Committee considered that the ICER of approximately £62,000 per QALY gained estimated by the ERG represented a more plausible (although still uncertain) ICER for the prior sunitinib group. For the prior cytokine population, the Committee concluded that the ICER of approximately £65,000 per quality-adjusted life year (QALY) gained (with the PAS applied in the evidence submission) may have been over-estimated, based on the unlikely overall survival (OS) with best supportive care (BSC) in this population, but that there were other uncertainties that might push the ICER higher.

We hold strong concerns about the analyses and assumptions used as the basis for the draft recommendation in the ACD. We do not believe that the ACD represents a sound and reliable assessment of the evidence and therefore appropriate guidance to the NHS. We are concerned that the NICE process has under-stated the value of axitinib.

We believe that the £62,000 per QALY ERG scenario in the prior sunitinib population is based upon the assumption that patients on axitinib will have no QALY/survival gains post-progression over BSC. This assumption is clinically implausible for the following reasons:

1. It is based on the biased prior cytokine survival estimates, which underestimate the benefit of axitinib over BSC due to the unlikely high estimated OS for BSC in this patient population. The Committee, clinical experts and patient groups considered these survival estimates to be clinically implausible.
2. Published evidence including data from Phase III randomised controlled trials (RCTs) comparing targeted therapies with BSC indicates that the post-progression survival (PPS) for targeted therapies is greater than the PPS for BSC, which is in-line with results of the STC in our base case analysis.
3. NICE has accepted in previous appraisals for second-line mRCC treatments that targeted therapies increase post-progression survival compared with BSC.

In addition, in order to address the Committee's concerns about the validity and reliability of the STC due to the lack of confidence intervals (CIs) or standard errors (SE) around the adjustment factors, we have further developed the STC methodology to estimate these CIs.

As previously stated, no QALY/survival gain post progression was observed in the base case for the prior cytokine population which resulted in an ICER of £65,326 per QALY gain for axitinib vs. BSC with the PAS in the evidence submission. However, this is not the most plausible ICER for decision-making as the axitinib survival and cost-effectiveness is underestimated due to the unlikely high estimated OS for BSC. In fact, when a more clinically plausible scenario was used for the OS with BSC the ICER for the updated analysis with the PAS in the evidence submission was £42,647.

In summary, the evidence and arguments provided support the robustness of the STC results and our base case cost-effectiveness estimates for axitinib. In the prior sunitinib population who represent the vast majority of second-line mRCC patients in the UK, our base case ICER for axitinib is lower than the accepted thresholds for other end-of-life treatments (with the PAS applied in the evidence submission). Overall, we believe that axitinib is clinically- and cost- effective treatment and should be recommended for second-line mRCC patients where there is significant unmet need as there are no NICE approved treatments.

1. Has all of the relevant evidence been taken into account?

1.1 Simulated Treatment Comparison Adjustment Factors, Confidence Intervals and Standard Errors

In Section 4.7 in ACD "*The Committee was aware that no confidence intervals or standard errors were provided to assess the uncertainties"* of STC. In section 3.20 "*The ERG also stated that the results of the comparison could not be verified because individual patient data from the AXIS trial were used; and the uncertainties around the results could not be assessed because standard errors and 95% confidence intervals were not presented".*

In order to address the ERG's and Committee's concerns about the validity and reliability of the STC due to the lack of CIs or SE around the adjustment factors, we have developed the methodology to estimate these CIs and SE, which is described in Appendix 1. This methodology should be considered along with the STC methodology described in Section 6.7.11 and Appendix 16 of the original evidence submission[1, 2]. The adjustment factors for which the CI and SE are estimated below in Appendix 1 are presented in Section 6.7.11 (page 103 and 106) and Section 7.3.6 (Table 40) of the original evidence submission[3-5].

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

For the prior sunitinib population, we believe that the ERG exploratory scenario considered more plausible by NICE, which resulted in a cost per QALY of £62,108 (with the PAS in the evidence submission), applies clinical assumptions that are unreasonable interpretations of the evidence. In responding to this question, we highlight the key elements of the STC and assess the validity of the results in the context of available clinical evidence. We then provide the clinical rationale to demonstrate why the assumptions underpinning the ERG exploratory scenario should be considered clinically implausible. Please note that in this scenario, the ERG assumed no difference in QALY gains for axitinib over BSC in the PPS period. This means that the PPS was assumed to be the same for both axitinib and BSC (i.e. no clinical or survival benefit of axitinib over BSC after the RECIST-defined progression period) based on the assumption used in our model that the utility values for the PPS period were the same for both axitinib and BSC.

QALY axitinib PPS = (axitinib PPS x utility PPS) = QALY BSC PPS= (BSC PPS x utility PPS), which results in axitinib PPS = BSC PPS

2.1 The Simulated Treatment Comparison

Given the importance of the STC results to this appraisal, we have summarised the key elements of the rationale for using this method followed by a brief description of the methodology and the results of the STC below.

2.1.1 Rationale and Background for the Simulated Treatment Comparison

The axitinib pivotal trial (AXIS) was performed against an active comparator, sorafenib (the only second-line licensed treatment at the time of the AXIS trial design); thus no direct comparative data are available for axitinib versus BSC for the prior sunitinib population. Importantly, it would be considered unethical with the availability of a licensed second-line treatment, both at the time of study design and now, to conduct a randomised clinical trial of an active therapy against placebo in second-line mRCC.

In addition, in the absence of direct comparative data, it was not feasible to perform the widely-used approach of an indirect comparison owing to the lack of available RCT evidence comparing sorafenib with BSC, which was acknowledged by the ERG.

As requested by NICE, BSC is the relevant comparator for this appraisal since no other second-line treatment for advanced RCC is currently recommended. To address the lack of direct and indirect comparative evidence of axitinib versus BSC, as acknowledged by the ERG, an STC was performed for the prior sunitinib population to enable a comparison of axitinib with BSC.

The STC is a statistical method that simulates the “missing arms” of a randomised trial. The STC methodology was the only robust option with the currently available evidence to compare axitinib with BSC in a prior sunitinib population, as acknowledged by the ERG. The Committee noted that the STC was based on a comparison of two single treatment arms without random allocations to treatment. It is important to recognise that the STC

methodology involves adjusting for differences between the populations in the arms of the two studies. This is a fundamental component of STC, which reduces the potential for bias. Therefore, it is incorrect to state that the STC methodology does not attempt to control for confounding factors, which is the purpose of treatment randomisation. This method also relies on the general comparability of the studies being considered; however, the same assumption applies to all other methods of indirect comparisons.

It is important to note that the ERG performed their own searches to try to bridge the gap between axitinib and BSC and found that it was not feasible with the available evidence. The RECORD-1 trial (a Phase III RCT that evaluated the safety and efficacy of everolimus versus BSC in mRCC patients who progressed on vascular endothelial growth factor (VEGF) receptor–tyrosine kinase inhibitor [TKI] therapy) was the only study identified by the systematic review that reported data on patients who received BSC following sunitinib treatment. The STC methodology utilises clinical trial data for BSC directly observed in the Phase III RCT, RECORD-1, and applies minor adjustments to account for the observed differences in the patient characteristics between RECORD-1 and AXIS (see Table 1).

Table 1: Differences in Patient Characteristics Between AXIS and RECORD-1

Prior sunitinib group	AXIS	RECORD-1	
	Axitinib[6] 194 (54%)[7]	**Everolimus**[6] 127 (45%)[8]	**Placebo**[6] 139 (100%)[8]
Age, median years (range)	61 (22–82)	59 (28–81)	60 (29–79)
Sex, % male	74%	80%	76%
ECOG/KPS			
0 / 90–100	**52%**	**60%**	**68%**
1 / 70–80	**48%**	**41%**	**33%**
2 / 50–60	0%	0%	0%
Missing	0%	1%	0%
MSKCC			
Favourable (0)	**20%**	**28%**	**28%**
Intermediate (1)	**41%**	**55%**	**57%**
Poor (≥1)	**36%**	**17%**	**15%**
Previous nephrectomy	88%	91%	96%[8]
Previous radiotherapy	23%	31%	27%[8]
Clear cell RCC	98%	100%	100%[9]
Metastatic sites			
Lung			81%[8]
Liver			38%[8]
Bone			30%[8]
Lymph node			70%[8]
Weeks on sunitinib	41.4 (2.7–471)	41.3 (1.3–120)	NA
Prior cytokine	0	Unknown (>0)	Unknown (>0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not applicable; RCC, renal cell carcinoma.

Several subgroup analyses of data from the RECORD-1 trial have been reported, including a pre-planned analysis of prior sunitinib patients who could also have had other non-VEGF treatments[10] and an exploratory analysis of patients who only had sunitinib as a first-line treatment before enrolling in the RECORD-1 trial[11] (See Table 2).

Table 2: Clinical Outcomes Reported in RECORD-1

		Placebo + BSC	Everolimus + BSC	HR (95% CI)
ITT population				
Prior VEGFR inhibitor ± systemic therapy*	Median PFS[8]	1.9 months (n=139)	4.9 months (n=277)	0.33 (0.25; 0.43, p<0.001)
	Median OS[12]	14.4 months (n=139)	14.8 months (n=277)	0.87 (0.65; 1.15, p=0.162)
ITT population RPSFT adjusted for crossover				
Prior VEGFR inhibitor ± systemic therapy*	Median OS	10 months	14.8 months	0.53
Subgroup by prior treatment				
Post sunitinib or sorafenib ± other systemic therapies*[13]	Median PFS	1.9 months (n=103)	5.4 months (n=205)	0.32 (0.24; 0.43, p<0.001)
	Median OS	NR	NR	NR
Post sunitinib± other systemic therapies*[14]	Median PFS	1.8 months (n=60)	3.9 months (n=124)	0.34 (0.23; 0.51, p=NR)
	Median OS	NR	NR	NR
Second-line post sunitinib only[13]	Median PFS	1.8 months (n=13)	4.6 months (n=43)	0.22 (0.09; 0.55, p<0.001)
	Median OS	NR	NR	NR
Second-line post sorafenib only[15]	Median PFS	1.9 months (n=12)	3.8 months (n=18)	0.35 (0.14; 0.88, p=0.010)
	Median OS	NR	NR	NR
Subgroup by intolerance to prior therapies				
VEGFR-intolerant[16]	Median PFS	1.9 months (n=13)	5.4 months (n=45)	0.32 (0.13; 0.77, p=0.004)

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reported; OS, overall survival; PFS, progression-free survival; RPSFT, rank-preserving structural time failure; VEGFR, vascular endothelial growth factor receptor.

**Prior therapies could also have included bevacizumab, cytokines, hormones or chemotherapy.*

For the STC, the ITT BSC arm of the RECORD-1 population was used as there were no OS data (adjusted for crossover) available from the pre-planned analysis for the prior sunitinib population (see Table 3). Considering the median PFS for BSC ranged from 1.8–1.9 months (8 weeks) across all subgroups in the RECORD-1 trial, using the ITT placebo PFS data for the prior sunitinib population is a reasonable assumption.

2.1.2 Simulated Treatment Comparison Results

Axitinib median PFS and OS data in the model were derived directly from AXIS patient-level data for the prior sunitinib population and have not been further adjusted to account for the differences in patient populations between the two trials. The STC approach aims to simulate the missing BSC arm in AXIS and estimate what would have been the PFS and OS outcomes for a population receiving BSC in AXIS, based on what has been observed in RECORD-1 trial.

Table 3: Observed and Adjusted (Parametric Modelling and Simulated Treatment Comparison) Progression-Free Survival and Overall Survival Estimates

Intervention	Survival method	Median PFS	Median OS	Absolute Ratio* Median PFS (months) : Median OS (months)
Axitinib	Kaplan-Meier[17]	4.8	15.2	1 : 3.2
	Fitted parametric model	5.8 (Weibull)	15.2 (lognormal)	1 : 2.6
	STC adjustment	N/A**	N/A	N/A
BSC	Kaplan-Meier	1.8	10.0	1 : 5.6
	Fitted parametric model	1.8 (Weibull)	10.0 (lognormal)	1 : 5.6
	STC adjustment	1.7 (Weibull)	8.3 (lognormal)	1 : 4.9

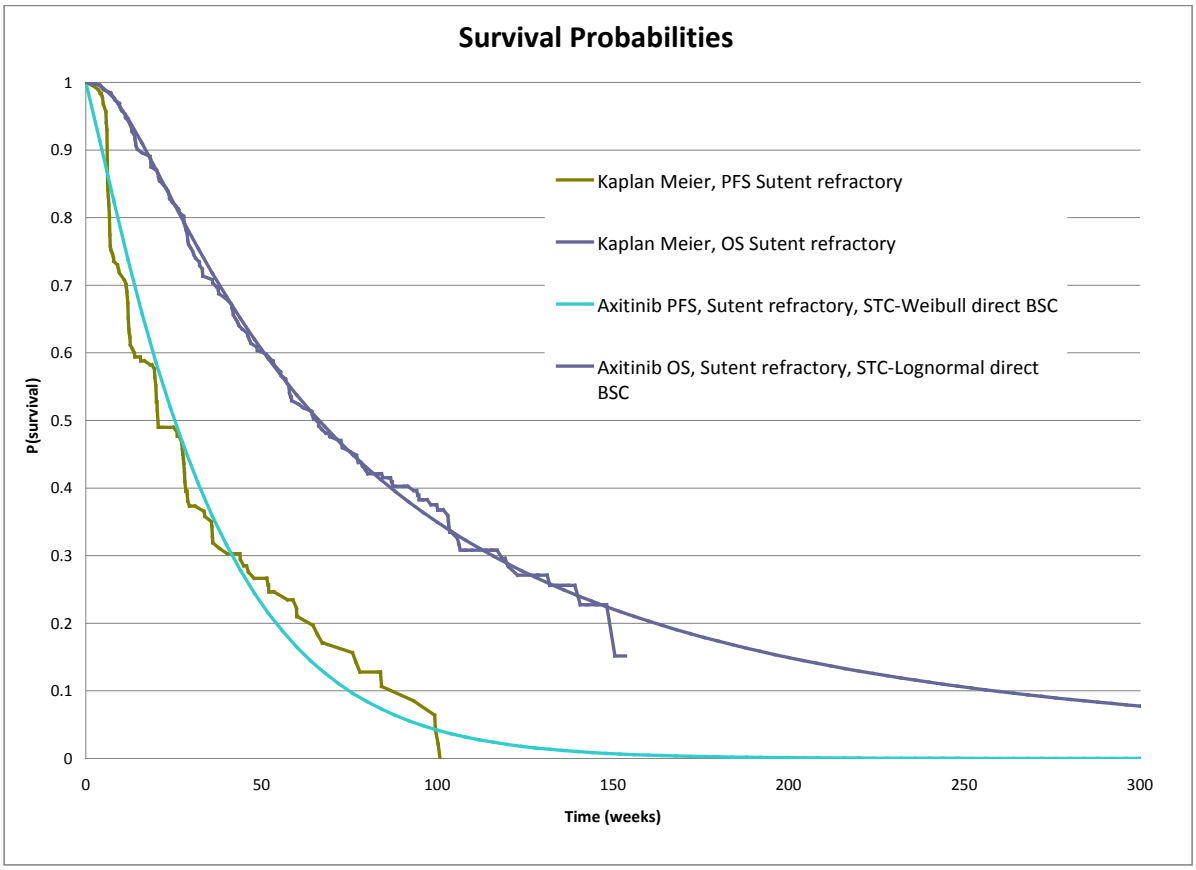
Abbreviations: BSC, best supportive care; N/A, not applicable; OS, overall survival; PFS, progression-free survival; STC, simulated treatment comparison.

**Ratio between axitinib PFS to axitinib OS; **No adjustment required for axitinib as RECORD-1 simulated to AXIS trial*

The first step in the STC was to estimate the survival of axitinib patients using AXIS clinical data. A number of distribution functions, including the exponential, Weibull, Gompertz, lognormal and loglogistic distributions (using Stata 10.0), were fitted to clinical survival data. The lognormal distribution provided the best fit for OS in axitinib patients who failed prior sunitinib in the AXIS trial. The lognormal curve had the best fit for PFS in the sunitinib-

refractory population, but as it resulted in a long tail at the end of the curve, which was considered clinically implausible (also based on the Kaplan-Meier data), the Weibull model, which was the second best-fit, was chosen as base case. The difference between median PFS (5.8 months Weibull versus 4.8 months Kaplan-Meier) was due to the process of fitting the parametric curve around the median point rather than the STC adjustments (See Figure 1).

Figure 1: Kaplan-Meier and Parametric Survival Distributions for Axitinib in the Prior Sunitinib Population



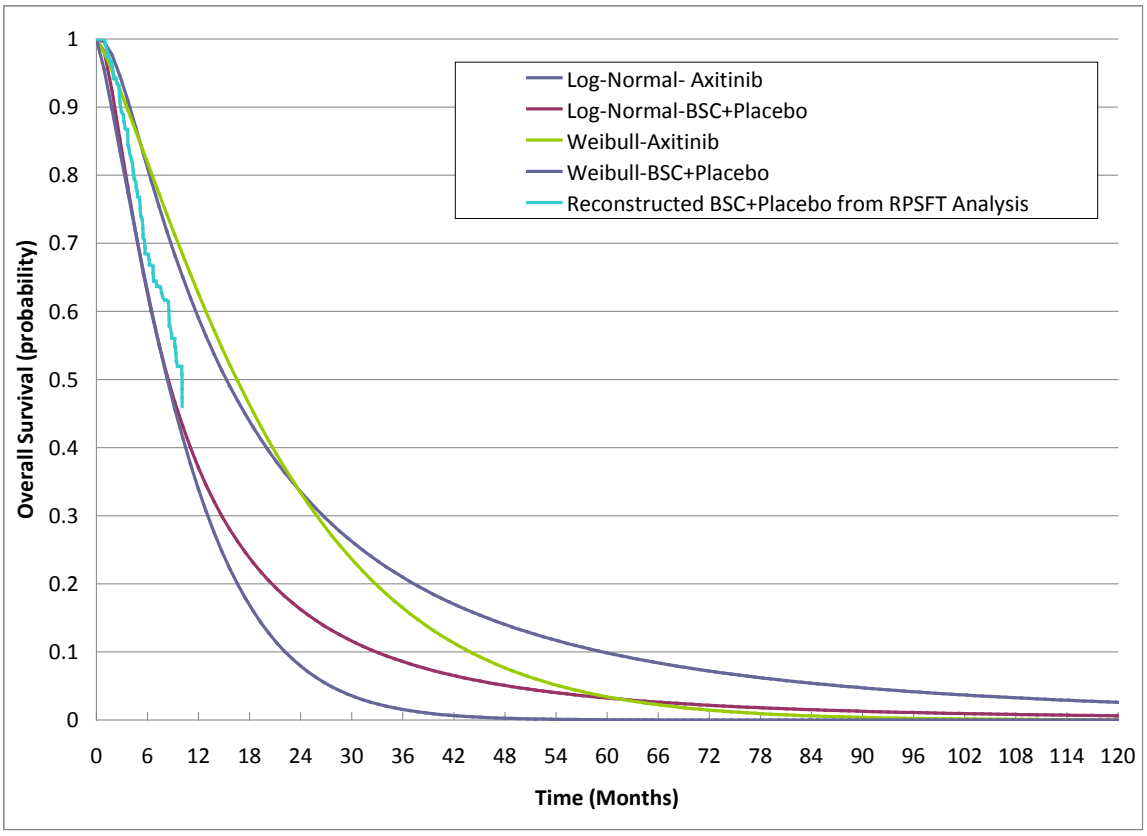
BSC OS and PFS data in the model were derived directly from the RECORD-1 ITT BSC median PFS and OS estimates. These estimates were subsequently adjusted with the STC methodology to account for the differences between AXIS and RECORD-1 in predictive factors for PFS (age and Memorial Sloan-Kettering Cancer Center [MKSCC]) and for OS (MKSCC and duration on prior sunitinib treatments) as identified by the multivariate analysis. As expected, worse MSKCC scores at baseline were negatively associated with PFS. Association of age with PFS is somewhat counter-intuitive since being older was associated with longer PFS. However, median age in the axitinib and everolimus arm was similar (59 vs 60 years – see Table 1), which means that inclusion of age has minimal impact on the adjustment factor derived from STC analyses. For OS, the estimated effects associated with prior duration of sunitinib therapy and MSKCC were consistent with expectations; worse performance score at baseline and shorter duration of prior sunitinib therapy were negatively associated with OS.

The STC adjustment factors decreased the median PFS estimate in the RECORD-1 ITT BSC by 0.1 month (1.7 months for STC versus 1.8 months in RECORD-1) and the median OS by 1.7 months (8.3 months for STC versus 10.0 months for RECORD-1). The Kaplan-Meier, parametric and STC-adjusted OS curves for axitinib and BSC in the prior sunitinib population are shown in Figure 2.

These adjustments aimed to make the RECORD-1 ITT BSC population comparable to the axitinib patient population in the AXIS prior sunitinib population, and primarily reflected the poorer MKSCC risk scores in the AXIS trial population compared with the RECORD-1 trial population (see Table 1).

These adjustments are clinically meaningful since the MKSCC prognostic model is currently the most widely used validated tool in predicting survival in advanced RCC, both in clinical practice and in clinical trials. The MKSCC model divides patients into three prognostic risk groups (favourable, intermediate and poor) with a statistically significant and clinically-relevant difference in OS between the groups[18]. A recent analysis of the AXIS data indicated that the MSKCC risk score was prognostic for Kaplan-Meier estimates of OS in the overall population[19].

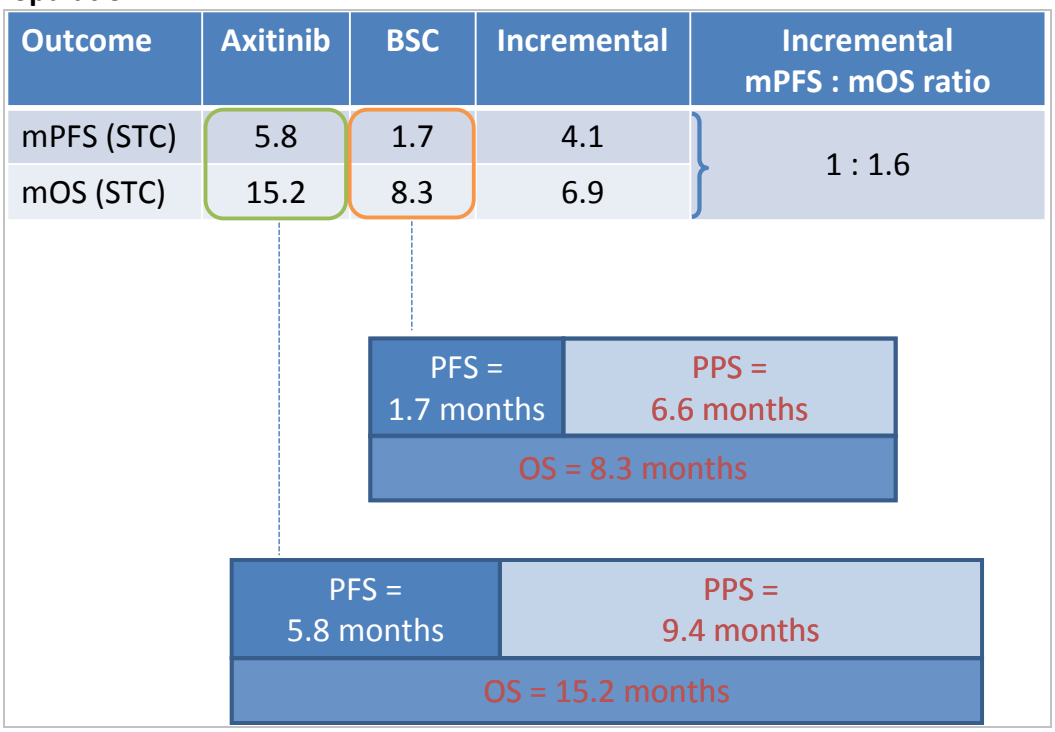
Figure 2: Kaplan-Meier, Parametric and Simulated Treatment Comparison-Adjusted Survival Curves for Axitinib and Best Supportive Care in the Prior Sunitinib Population



The STC produced an estimated median PFS of 1.7 months for axitinib-like patients if they had received BSC, compared with 5.8 months for axitinib. The estimated median OS was 8.3 months for axitinib-like patients, assuming that they received BSC, compared with 15.2

months for axitinib. Overall, in the sunitinib-refractory population, axitinib improved median PFS by 4.1 months and median OS by 6.9 months, compared with BSC (see Table 4). The PPS was 9.4 months for axitinib versus 6.6 months for BSC, corresponding to a PPS gain of 2.8 months. Therefore, additional survival benefits for axitinib over BSC were shown before (4.1-month gain) and after (2.8-month gain) progression. The results of our base case cost-effectiveness analysis showed that there were additional QALY gains with axitinib before (4.1 months gain multiplied by PF utility of 0.692) and after (2.8 months gain multiplied by PD utility of 0.61) progression versus BSC. As stated in the ACD, the majority of the additional QALYs gained were observed before progression; this is due to the greater incremental benefit in PFS versus PPS for axitinib over BSC (see Figure 3).

Figure 3: Base Case Progression Free and Overall Survival Results in the Prior Sunitinib Population



Median PFS and OS data from Pfizer submission of evidence[20]

2.1.3 Simulated Treatment Comparison Results are in Line with Evidence from Other Phase III Clinical Trials in Second-Line mRCC

In order to place the STC results in the context of other Phase III data following prior therapies, the relationship between PFS- and OS-gain observed in other Phase III RCTs comparing active treatments with BSC was explored. These robust trials have shown that: 1) the active targeted therapy achieves survival gains by increasing the PFS period (i.e. PFS) over BSC, and 2) additional survival gains are also achieved over BSC after progression in the PPS period. While comparisons across clinical trials are difficult, owing to differences between studies, we have examined the survival gain of active targeted therapy versus BSC as a ratio of PFS gain to OS gain over BSC. This method provides a common ratio to assess the plausibility of the STC results versus currently available Phase III RCT data.

For example, the STC results estimated a gain of 4.1 months in median PFS and a gain of 6.9 months in median OS for axitinib over BSC. This corresponds to 1 to 1.6, PFS gain to OS gain relationship, which suggests that a 1-month PFS gain is associated with a 0.6-month PPS gain, resulting in a total of 1.6 months of OS gain (Table 4).

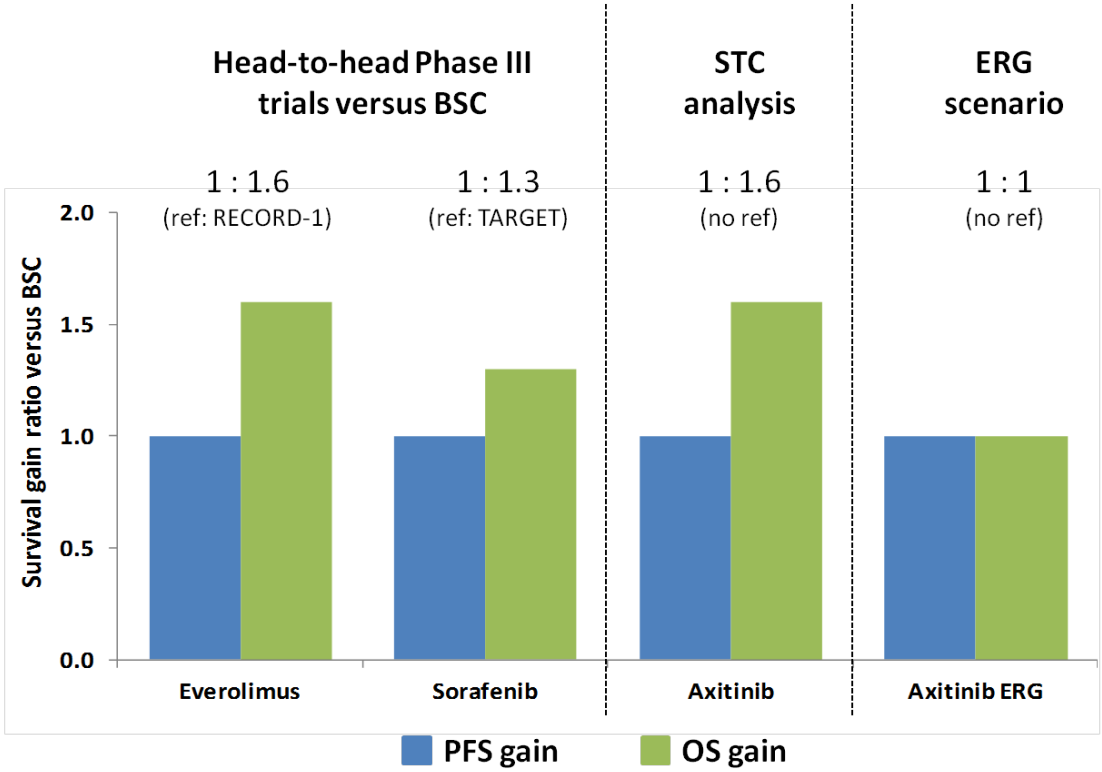
Table 4: Observed and Adjusted (Parametric Modelling and Simulated Treatment Comparison) Progression-Free Survival and Overall Survival

Outcome	**Active treatment**	**Placebo/BSC**	**Gain**	**mPFS gain : mOS gain ratio***
AXIS (STC)				
Outcome	Axitinib	Placebo/BSC	Gain	mPFS gain : mOS gain ratio
Median PFS (STC weibull)	5.8	1.7	4.1	1 : 1.6
Median OS (STC lognormal)	15.2	8.3	6.9	
RECORD-1				
Outcome	Everolimus	Placebo/BSC	Gain	mPFS gain : mOS gain ratio
Median PFS (ITT)	4.9	1.9	3.0	1 : 1.6
Median OS (RPSFT adjusted for crossover)	14.8	10.0	4.8	
TARGET				
Outcome	Sorafenib	Placebo/BSC	Gain	mPFS gain: mOS gain ratio
Median PFS (ITT)[21]	5.5	2.8	2.7	1 : 1.3
Median OS (censored adjusted for crossover)[22]	17.8	14.3	3.5	

Abbreviations: BSC, best supportive care; ITT, intention to treat; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; RPSFT, rank-preserving structural failure time; STC, simulated treatment comparison.

**Ratio of PFS gain (over BSC) to OS gain (over BSC)*

Figure 4: Progression Free to Overall Survival Gain Ratio Versus Best Supportive Care



The survival gain ratio for each targeted agent used as second-line therapy for RCC was calculated using published data from clinical trials (RECORD-1 [everolimus][23] and TARGET [sorafenib][21, 22]), data derived from the STC analysis or data recommended from the ERG[24]. Survival gain for each targeted agent was calculated using: (difference in median OS between the targeted agent and BSC)/(difference in median PFS between the targeted agent and BSC), with the results expressed as a ratio of median PFS.

In RECORD-1 and TARGET, which both compare an active targeted therapy versus BSC, it was observed that for every 1-month gain in PFS for everolimus or sorafenib over BSC, there was a 1.3-month and 1.6-month gain in OS over BSC, respectively (see Figure 4).

For the TARGET trial, this range is potentially an underestimation since the 1.3-month OS gain per 1-month PFS gain observed for sorafenib over BSC would likely have been higher if the BSC arm of TARGET was adjusted for crossover using a more appropriate method than censoring (i.e. RPSFT). This has been acknowledged by NICE, with the ACD stating that "*the overall survival of 14.3 months in the placebo arm of TARGET was not properly adjusted for crossover"* (Section 4.12 NICE ACD)[25].

In addition to the relationship observed in the RECORD-1 and TARGET trials, a meta-analysis of 28 trials of a range of treatments for advanced RCC (8770 patients) explored the relationship between PFS and OS[26, 27]. In this study, a subgroup analysis found an OS benefit of 1.61 months (95% CI: 0.7; 2.52) per 1-month gain in PFS for the 24 studies without crossover from placebo to active treatment. The OS benefit was 1.42 months (95% CI: 0.34; 2.51) per 1-month PFS in the 16 studies in which patients had received prior therapy. The manufacturer stated that the survival benefit of 4.9 months in RECORD-1 (for everolimus plus BSC versus placebo plus BSC) obtained from the RPSFT analyses was in line with the survival benefit hypothesised from this meta-analysis.

It is important to note that in the final appraisal determination for the everolimus appraisal NICE stated that "*The Committee noted the meta-analysis submitted by the manufacturer and accepted that a 1.4-month increase in overall survival per 1 month increase in progression-free survival for patients with advanced RCC who had received prior therapy was plausible"* (Section 4.5)[27]. This relationship (PFS gain:OS gain ratio of 1:1.4) suggests that a 1-month PFS gain is associated with a 0.4-month PPS gain, resulting in a total of 1.4 months of OS gain. In addition, *the Committee accepted that the incremental survival using the RPSFT analysis* (1:1.6, 1.6-month increase in OS per 1 month increase in PFS) *and corresponding ICER was plausible*. Therefore, in the everolimus appraisal, the NICE committee accepted that a PPS gain is plausible for an active comparator versus BSC in second-line mRCC.

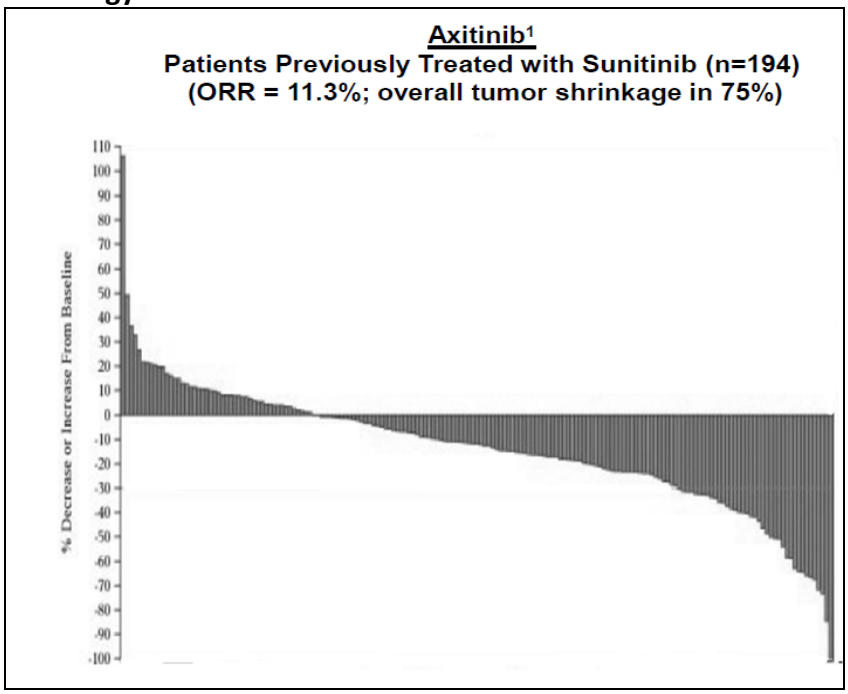
This PFS:OS relationship is anticipated when active targeted therapies are compared with BSC. Active treatments not only prolong the PFS but simultaneously prevent the worsening of disease and, in some situations, achieve a reduction in tumour burden compared with patients receiving BSC who are expected to further progress rapidly and their clinical condition to deteriorate.

Additionally, progression in AXIS and RECORD-1 was defined by tumour growth according to RECIST criteria, which represent the standard tumour response measurement used for clinical trials and in clinical practice. While this serves as a simple objective endpoint for tumour response evaluation in clinical trials and can be used worldwide, it was developed in the era of chemotherapy and does not easily translate to the era of targeted therapy. As axitinib is associated with higher response rates (see Figure 5) and tumour shrinkage than BSC (see Figure 6) at the point of progression, patients who progress on axitinib would be expected to have longer PPS (i.e. live longer after progression) than patients who progress on BSC. Targeted therapies frequently induce disease stabilisation as defined by RECIST rather than a substantial reduction in tumour size. Potent targeted therapies, such as axitinib, can cause early/extensive tumour necrosis without a marked decrease in size and, therefore, a good clinical response may be underestimated by RECIST criteria[28-30]. In some cases, the development of tumour necrosis may even be accompanied by an increase in tumour size, thereby mimicking progressive disease according to RECIST criteria. This scenario potentially ignores the fact that patients may be obtaining clinical benefit from active treatment, beyond RECIST-defined disease progression by extending into the PPS period.

In patients who exhibit a response according to RECIST criteria, a 20% reduction from baseline is defined as a partial response. Recent evidence has suggested that tumour shrinkage of 10% or greater is predictive of OS. In one retrospective multivariate analysis, tumour shrinkage of 10% or greater within 12 weeks of treatment proved to be a significant independent prognostic (hazard ratio [HR] 0.361; 95% CI: 0.156–0.833) and predictive (HR 0.306; 95% CI: 0.152–0.612) parameter, when tested with other common variables, such as ECOG performance status, MSKCC risk score, histology and metastatic sites[31]. In addition, evidence from the same study suggests that tumour shrinkage of 10% or greater results in greater median progression free and post progression survival. Furthermore, recent evidence from a multivariate analysis has shown that tumour burden at baseline is a predictor of OS, independent of the site of metastases and the MSKCC risk score[32]. Therefore, a patient who experiences a response to treatment will have a decreased tumour burden at the point of progression versus baseline, compared with a patient who has not responded (i.e. they will have a decreased or the same tumour burden versus baseline). As

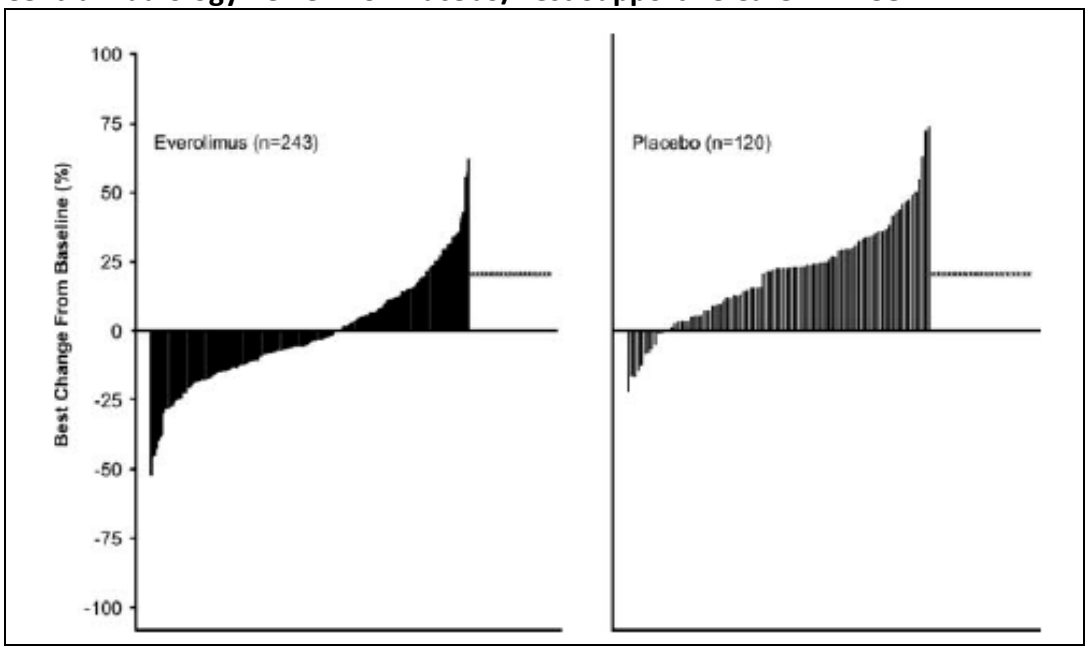
axitinib is associated with higher response rates (see Figure 5) and tumour shrinkage than BSC (see Figure 6) at the point of progression, patients who progress on axitinib would be expected to have longer PPS (i.e. live longer after progression) than patients who progress on BSC.

Figure 5: Percentage Change from Baseline in Sum of Longest Diameters Based on Central Radiology Review for Axitinib in AXIS



Source: Rini et al, 2011

Figure 6: Best Percentage Change from Baseline in Sum of Longest Diameters Based on Central Radiology Review for Placebo/Best Supportive Care in RECORD-1

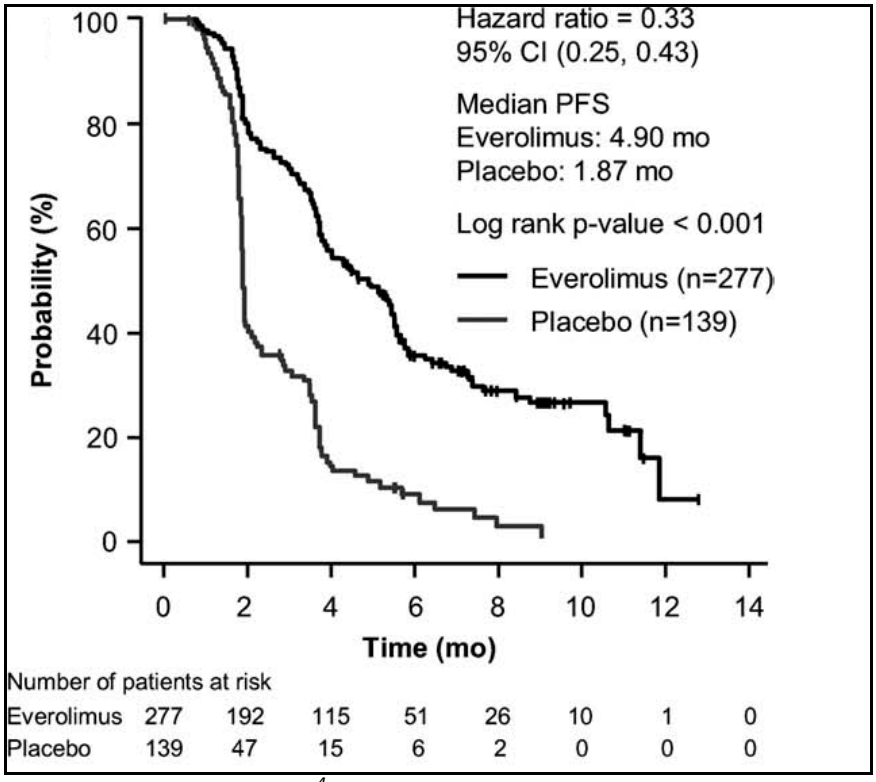


Source: Motzer et al, 2010

In our model, PFS and PPS were defined according to RECIST criteria. Therefore, as demonstrated above, it is expected that patients who progress on axitinib will continue to derive benefit from having been treated with axitinib and have a PPS gain versus patients who progress on BSC. This is in line with the STC estimates for PFS and OS gains of axitinib versus BSC in the prior sunitinib population.

Furthermore, it is important to note that PFS and OS gains, as estimated by the STC, are potentially underestimated since the first tumour assessment using the RECIST criteria in RECORD-1 trial was 8 weeks from enrolment (median PFS 1.8–1.9 months = 8 weeks). This suggests (see Figure 7), that a large proportion of patients receiving BSC would have progressed between 0 and 8 weeks and, therefore, the median PFS is likely to have been overestimated in RECORD-1.

Figure 7: Kaplan-Meier Estimates of Progression-Free Survival by Central Radiology Review



Source: Motzer et al, 2010[4]

[redacted]

[redacted]

All the clinical evidence described above indicate that a survival gain for axitinib versus BSC, both before and after progression, is clinically plausible and is directly incongruent with the clinical assumptions that underpins the ERG exploratory scenario, which the Committee has considered more plausible. The axitinib ACD stated that "*For the prior-sunitinib population, the Committee noted the clinical implausibility of the QALY gains accumulated after progression in this group of people"* (Section 4.15)[35]. In addition, the ACD stated that "*The Committee considered that the ICER of approximately £62,000 per QALY gained estimated by the ERG represented a more plausible (although still uncertain) ICER for the prior-sunitinib group"* (Section 4.15)[35]*.* In this scenario for prior sunitinib patients, the ERG assumed that a 1-month PFS gain for axitinib versus BSC is associated with no PPS gain, resulting in a total of 1 month of OS gain. Based on the evidence discussed above, we disagree with the ERG's assumption of no PPS gain for axitinib over BSC, especially given that their assumption seems to be based on the prior cytokine results, which are over-estimated due to inappropriate adjustment for cross-over in TARGET.

2.2 Evidence Review Group Additional Exploratory Analysis is Clinically Implausible and Inconsistent with Conclusions in Previous mRCC Appraisals and Committee's Conclusions for the Cytokine Refractory Results

The ERG additional exploratory analysis was driven by how QALYs accumulate in our base case analysis for axitinib versus BSC before and after progression for the two subgroups (i.e. cytokine-refractory and sunitinib-refractory patients). They noted that in our base case analysis for the cytokine-refractory patients the number of QALYs accumulated after progression are the same for the axitinib and BSC arm, and therefore there was no QALY gain for axitinib over BSC. Given that the utilities used in the model were assumed to be the same for both axitinib and BSC before and after progression, no QALY gain post progression means no survival gain post progression. As noted above, this is in contrast to what has been reported in other second-line mRCC clinical trials, which have compared targeted therapies with BSC, and what is estimated by the STC analysis for the prior sunitinib patients. Based on the clinical data and rationale described above, it is anticipated that a targeted therapy such as axitinib, when compared to BSC, will result in survival gains both before and after progression.

Importantly, in section 4.12 of the ACD *the Committee discussed the plausibility of the survival gains estimated for the prior-cytokine group from the economic model. The Committee heard from the clinical specialists and patient experts that the overall survival of approximately 24 months in the best supportive care group of the prior-cytokine group is not seen clinically. It noted the manufacturer's comment that the implausibility observed may have resulted from the overall survival of 14 months in the placebo arm of TARGET which was not properly adjusted for crossover. The Committee considered that this possible over-estimation of the overall survival of BSC in TARGET was carried over into the overall survival*

results in the indirect comparison and ultimately affected the model results for the best supportive care group.[25] Therefore, the overestimation of the PPS in the BSC arm in TARGET, which was due to 48% of patients crossing over to sorafenib, resulted in an underestimation of the PPS gain of axitinib versus BSC. This provides a clear rationale as to why, in our base case results for the prior cytokine patients, there was no PPS gain (i.e. no QALY gain) for axitinib over BSC.

In addition, a median OS of 24 months would have been clinically implausible even in first line mRCC patients receiving cytokines where response to treatment is only seen in a small select population. Of note, the NICE appraisal of sunitinib for the first-line treatment of mRCC patients was based on an OS analysis which estimated that the median OS for cytokine patients who have not received post-study treatments was around 14 months.

Despite this clear rationale, the ERG questioned whether there is a good reason why prior sunitinib patients receiving axitinib would have a QALY gain compared with BSC after progression, while prior cytokine patients do not. Thus they performed a scenario analysis in which it was assumed that for the prior sunitinib patients there was no difference in survival benefit after progression. This approach resulted in an ICER of approximately £62,108 per QALY gained (with the PAS applied in the evidence submission). Subsequently the NICE appraisal committee considered that this scenario explored by the ERG represents a more plausible (although still uncertain) ICER for the prior-sunitinib group, and concluded that axitinib could not be considered to be a cost-effective use of NHS resources, as the ICER of £62,108 (with the PAS applied in the evidence submission) would have been higher than previously acceptable ICERs for end-of-life treatments.

The ERG exploratory analysis and the NICE appraisal committee draft recommendation is therefore inconsistent to what the Committee concluded regarding the results of our base case for the prior cytokine population, acknowledging the unlikely high OS for BSC. Therefore, the Committee and the ERG used the lack of PPS gains for axitinib versus BSC in the prior cytokine population, which were considered to be underestimated and clinically implausible by clinical experts, patient groups and the Committee itself to adjust the prior sunitinib results. It is important to note that clinical experts and patients groups during the Committee found the STC results to be clinically plausible. In addition, in section 2.1.3 above, the STC findings were found to be consistent with clinical evidence from second-line mRCC trials comparing targeted therapies with BSC.

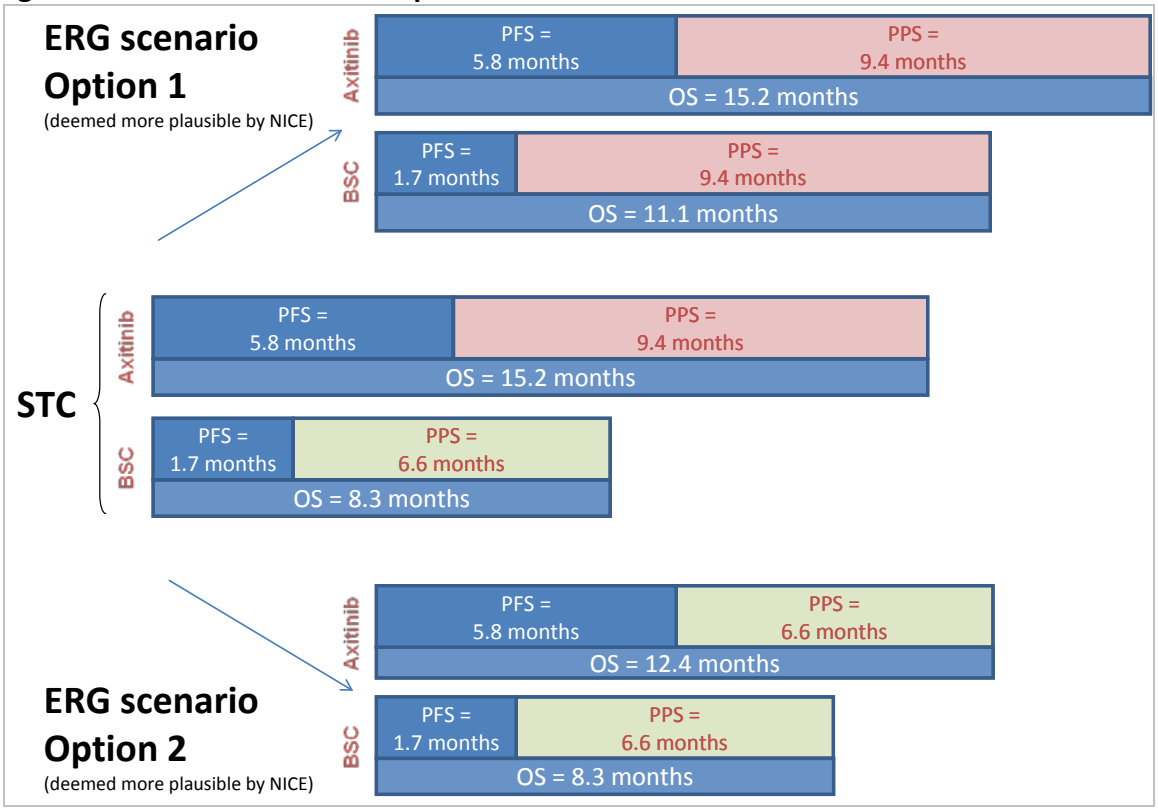
Furthermore, the ERG did not provide sufficient information regarding the assumed PPS for axitinib and BSC in this scenario. This, therefore, did not allow for assessment of the clinical plausibility of the necessary assumptions and adjustments to the estimates of OS for axitinib and BSC (which would have resulted in no QALYs post progression).

In addition to the inconsistencies of the ERG exploratory analysis identified above, in order to further assess the internal and external validity of the ERG exploratory analysis we have identified two likely scenarios for the adjusted PFS and OS estimates for axitinib and BSC, assuming no QALY/survival gain post progression. These scenarios were identified based on PPS estimates in the STC, which reflect the Phase III RCTs for axitinib and BSC in the prior sunitinib population. Given that only the AXIS and RECORD-1 trials reported survival estimates for axitinib and BSC, respectively, the PPS in the ERG exploratory analysis would have been either approximately 9.4 months (15.2 months OS – 5.8 months PFS for axitinib in

STC) or 6.6 months (8.3 months OS – 1.7 months PFS for BSC in STC) for both axitinib and BSC.

Assuming 9.4 months PPS, the OS in the ERG exploratory analysis would have been approximately 15.2 months (5.8 months PFS + 9.4 months PPS) for axitinib and approximately 11.1 months for BSC (1.7 months PFS + 9.4 months PPS). Assuming 6.6 months PPS, the OS in the ERG exploratory analysis would have been approximately 12.4 months (5.8 months PFS + 6.6 months PPS) for axitinib and approximately 8.3 months for BSC (1.7 months PFS + 6.6 months PPS) – see Figure 8.

Figure 8: Evidence Review Group Scenarios



Real-world evidence suggests that the median OS of patients on BSC following progression on sunitinib in the UK ranges from 4 to 6 months, which was previously highlighted in the everolimus NICE submission. Therefore, the results in ERG scenario 1 (Figure 8) over-estimate the survival on BSC. The BSC OS estimate in scenario 1 is also higher than the median OS with RPSFT (10.0 months) in ITT RECORD-1 BSC patients who had better MSKCC score, and thus further questioning the validity of the assumptions used in this exploratory analysis. In addition, axitinib OS in ERG scenario 2 was 12.4 months, which is inconsistent with the median OS estimate of 15.2 months from the AXIS study for prior sunitinib patients.

2.3 Sensitivity Analyses Results for the Prior Cytokine Population Suggests Base Case Incremental Cost-effectiveness Ratio is Overestimated

Section 3.41: Given the result of the sensitivity analyses, the ERG concluded that the model for the prior cytokine group was not very robust, with respect to most of the structural assumptions.

The ERG undertook exploratory analyses within which adjustments were made to some of the parameters used in the manufacturer's base-case sensitivity analysis. It varied the model input parameters using the 95% CI provided by the manufacturer in response to the ERG and NICE clarification questions. The most evident difference from the manufacturer's analysis was observed when the OS hazard ratio for the prior cytokine group was varied. The manufacturer's base-case result of £65,326 per QALY gained was very sensitive to this change, which resulted in an ICER range £42,647–423,083 per QALY gained (with the PAS applied in the evidence submission).

In section 4.12 of the ACD *the Committee discussed the plausibility of the survival gains estimated for the prior-cytokine group from the economic model. The Committee heard from the clinical specialists and patient experts that the overall survival of approximately 24 months (in the base case) for the best supportive care group of the prior-cytokine group is not seen clinically. It noted the manufacturer's comment that the implausibility observed may have resulted from the overall survival of 14 months in the placebo arm of TARGET which was not properly adjusted for crossover. The Committee considered that this possible over-estimation of the overall survival of best supportive care in TARGET was carried over into the overall survival results in the indirect comparison and ultimately affected the model results for the best supportive care group*[25].

Therefore, the overestimation of the OS in the BSC arm in TARGET in the base case, which was due to 48% of patients crossing over to sorafenib, resulted in an underestimation of the OS gain of axitinib versus BSC in the base case. This provides a clear rationale as to why moving the conservative OS HR for axitinib used in the base case to higher values within the 95% CI will result in even more clinically implausible OS scenarios for BSC. For example, in the scenario when the upper limit of the 95% CI for the OS HR is used, which results in an ICER of £423,083 (in the base case in the evidence submission), the median OS for patient receiving BSC is more than 30 months (with a PFS of 3.7 months). The ICER and survival estimates for the PAS in the evidence submission, for lower and higher 95% CI values for the OS HR in the indirect comparison are shown in Table 5.

Table 5: Incremental Cost-effectiveness Ratio and Survival Estimates for the Mean, Lower and Higher 95% CI Values for the Overall Survival Hazard Ratio in the Indirect Comparison

OS HR	Survival	Axitinib (median months)	BSC (median months)	Gain (median, months)	PFS gain: OS gain ratio	ICER (with PAS in the evidence submission)
0.63 (Base case)	PFS	11.5	3.7	7.8	1:1.1	£65,326
	OS	33.3	24.0	7.3		
0.99	PFS	11.5	3.7	7.8	N/A	£423,083

(Upper 95% CI)	OS	33.3	33.3	0		
0.41	PFS	11.5	3.7	7.8	1:1.8	£42,647
(Lower 95% CI)	OS	33.3	17.6	15.7		

Abbreviations: BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival.

When the lower 95% CI for OS HR was used, the OS for BSC in the prior cytokine population was 17.6 months which is close to the 14 months reported in TARGET. In this scenario, the PFS and OS results are in line with the findings above, which indicate that the PPS should be greater for axitinib over BSC. The ICER for this scenario was £42,647 with the PAS in the evidence submission, which is close to the base case ICER in the prior sunitinib population.

2.4 Rationale for Selection of Survival Distributions for Progression-Free Survival and Overall Survival

'Section 3.38: The ERG accepted the manufacturer's choice of the distributions used in the base-case and scenario analysis. However, it noted that in some cases, the method of selection of the distributions (based on the Akaike and Bayesian information criteria, visual inspection and anchoring) was unclear, with expert opinion always dominating the reason for selection, and, in one instance, the decision was based on expert opinion of clinical plausibility.'

To model axitinib efficacy data, PFS and OS were incorporated into the economic model using parametric survival curves to determine the proportion of patients in the PF, PD and death health states. The framework used follows the approach recommended in the NICE Decision Support Unit technical support document number 14.

Patient level data on PFS and OS were based on the most recent June 2011 and November 1, 2011 data cut-off respectively. Patient-level data were analysed using, exponential, Weibull, Gompertz, lognormal and loglogistic distributions (using Stata 10.0). Data were fitted to the clinical survival data for the axitinib treatment arm separately for the cytokine refractory and sunitinib refractory subgroups (sorafenib data were not included as it is not a relevant comparator for the model). Of the five distributions tested, the three judged the best fits were included in the model, with the base case representing the most plausible survival estimate, and the two scenario analyses representing alternate options.

To determine the best model fit, the following criteria were considered, with the most appropriate model identified based on a combination of these:

- AIC/BIC – Model fits were evaluated using Akaike's information Criteria (AIC) and Bayesian Information Criteria (BIC) statistics. Lower AIC/BIC figures are indicative of a better statistical fit of the survival function of the Kaplan-Meier data
- Visual Inspection – Visual inspection was carried out by plotting the projected survival curves overlaid with the Kaplan-Meier survival functions. Estimates were evaluated based on the goodness-of-fit of the parametric survival curve to the Kaplan-Meier curve during the trial period, and the clinical plausibility of the proportion of patients estimated to be surviving at the tails of the curve. Fits were

first assessed by the economic modelling team and validated using clinical input from UK expert clinical opinion.

- Anchoring – Wherever possible, extrapolation estimates were validated through comparison with more mature external data sources.

The selected distributions for the base case in the cytokine- and sunitinib-refractory populations, along with the parametric model that had the best statistical fit, are shown in Table 6.

Table 6: Selected Distributions for Axitinib

	Survival	Cytokine refractory	Sunitinib refractory
Base case	PFS	Weibull	Weibull
	OS	Weibull	Lognormal
Best fit (AIC/BIC)	PFS	Weibull	Lognormal
	OS	Weibull	Lognormal
Best fit (AIC/BIC) Proportional hazard model	PFS	Weibull	Weibull
	OS	Weibull	Weibull

Abbreviations: AIC, Akaike's information Criteria; BIC, Bayesian Information Criteria; OS, overall survival; PFS, progression-free survival.

Overall, for three of the four curves that were fitted, the final choice for base case coincided with the curve showing the best statistical fit. Only for the PFS curve in the sunitinib-refractory group was the choice of the distribution used in the base case based on expert opinion rather than the best statistical fit, as this was considered clinically more plausible. The lognormal curve had the best fit, in terms of AIC and BIC for PFS in sunitinib-refractory population, but as it resulted in a survival estimate at the tail-end of the curve (considered clinically implausible), the Weibull model (was the second best-fit and produced an intermediate PFS estimate between lognormal and Gompertz), was chosen as base case.

2.5 Therapeutic Value of Using Axitinib After Failure of Prior Sunitinib

Section 4.5: The Committee also noted the comment from the Committee for Medicinal Products for Human Use members that there were uncertainties over the therapeutic value of using axitinib after failure of prior sunitinib and the rationale for preferring axitinib over everolimus in this group of people[36].

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a positive opinion by absolute majority, recommending the granting of a marketing authorisation for axitinib after failure of prior treatment with sunitinib or a cytokine. In discussing the benefit-risk balance in the European Public Assessment Report, the CHMP stated that '*Treatment with axitinib showed an improvement in the median progression free survival. Results in ORR supported the observed improvement in PFS.*

Axitinib showed a clear antitumour effect in patients with advanced RCC that have failed prior cytokine and sunitinib therapy. The results are considered to be mature, robust and of clinical relevance.

Based on the safety data from the submitted studies, axitinib seems to be acceptably tolerated as monotherapy in patients with advanced RCC. There does not seem to be more AEs in subjects treated with axitinib compared to sorafenib, although the incidences of some of the individual AEs varies between the two treatment arms. The majority of adverse events were mild or modest in severity and relatively few patients discontinued therapy due to AEs.'[37]

We would like to clarify that the above comment in the ACD relates to a minority divergent opinion of four CHMP members to the majority recommendation, appended to the European Public Assessment Report.

In the view of this minority, there were uncertainties over the therapeutic value of using axitinib after failure of prior sunitinib and the rationale for preferring axitinib over everolimus in this group of people.

In relation to everolimus, it must be noted that everolimus was not licensed at the time of the trial design; AXIS was the first trial to compare against an active comparator, sorafenib, in second-line mRCC. There are no comparative Phase III RCT data for axitinib versus everolimus for patients with advanced second-line mRCC. Of note, as stated in the ACD, everolimus is not a comparator for this appraisal.

The European Society of Medical Oncology (ESMO) has recently updated the 'Renal Cell Carcinoma: ESMO Clinical Practice Guidelines (CPG) for diagnosis, treatment and follow-up'[38]. These guidelines are intended to provide the user with a set of recommendations for the best standards of cancer care, based on the findings of evidence-based medicine. Each CPG includes information on the incidence of the malignancy, diagnostic criteria, staging of disease and risk assessment, treatment plans and follow-up. In these guidelines axitinib is recommended as a standard second-line treatment option, with the highest level of evidence[38].

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

We believe the Committee's draft recommendation is based upon a clinically implausible scenario, which assumes that patients on axitinib will have no QALY/survival gains post progression over BSC. We, therefore, have concerns about the draft recommendation in the ACD and we strongly believe that it is not a sound and suitable basis for guidance to the NHS. In fact, taking the above findings into consideration, there is strong evidence to support the clinical plausibility of the STC results, which indicate that the PPS is greater for axitinib over BSC. This is in-line with results reported in Phase III trials of active treatments versus BSC and consistent with what a NICE committee has previously considered plausible for second-line mRCC.

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Appendix 1: Simulated Treatment Comparison Adjustment Factors, Confidence Intervals and Standard Errors

A1. Deriving 95% Confidence Interval for the Comparison Measure (δ)

The comparison measure (adjustment factor) can be expressed as the difference between the logarithm of the median OS/PFS of the comparator arm and logarithm of the predicted median time of comparator-like population had they received axitinib. In other words, the comparison measure is the difference between ln(t_c) (where t_c is the median OS or PFS) $\ln(t_c)$and the logarithm of the predicted median time from the axitinib equation, with values of the predictors set to the mean values of the comparator population.

Therefore, the variance of the comparison measure is a compound of the uncertainty from the derived axitinib equation and the uncertainty around the target value. The variance of the predicted median time for the comparator-like population, had they received axitinib, was derived using the variance–covariance matrix of parameters from the axitinib equation. To derive the variance of the logarithm of the median time, the delta method was applied (e.g. if y=log[x], then var[y] = [1/x]^2*var[x]). The variance of logarithm for the median OS and PFS of the comparator arm was derived using published materials as follows:

For BSC:

A median PFS of 1.8 months for prior sunitinib patients in the BSC arm in RECORD-1 trial was reported by Motzer 2010[14]. However, SE and 95% CI are not available and, therefore, the SE of median PFS for the entire BSC cohort was inflated by $\sqrt{2.3}$ (i.e. $\sqrt{139/60}$) to account for the fact that only 43% of the patients in the entire BSC were sunitinib refractory in the RECORD-1 trial.

Median crossover-adjusted OS of 10.0 months from rank-preserving structural failure time (RPSFT) analysis for the entire BSC cohort was reported by Motzer 2010[12], but SE and 95% CI are not available. To calculate the approximate SE, the 95% CI for the acceleration factor ψ^{ψ} derived from RPSFT analysis, reported by Korhonen 2012[39], was used. The median OS of everolimus (i.e. 14.8 months) was multiplied by exp($\psi_{LB}\psi_{LB}$) and exp($\psi_{UB}\psi_{UB}$) to estimate the lower (LB) and upper bound (UB) of the 95% CI for crossover-adjusted median OS for the BSC group, respectively. The SE for crossover-adjusted median OS was then derived as (ln[UB]–ln[LB])/(1.96*2).

Given that many assumptions were required to derive the SE of the median PFS/OS for the BSC population in the RECORD-1 trial, an alternative 95% CI for the comparison measure was calculated by only considering uncertainty in the derived axitinib equation and not for uncertainty in the estimated median PFS/OS for the BSC population in the RECORD-1 trial. It is important to note that the NICE committee in the everolimus appraisal was aware *that crossover also occurred in the RECORD-1 trial, although this was adjusted using the RPSFT method which both the manufacturer and the ERG considered to be appropriate*[40].

For Everolimus:

The median (95% CI) PFS and OS for prior sunitinib everolimus patients in RECORD-1 were taken from Di Lorenzo 2011[11] and Motzer 2010[14]. Log-Log transformation was applied to derive SE of log-log median time. The delta method[41] was then used to derive SE for the log median time.

Table A1: Adjustment factor for Progression-Free Survival for Axitinib-like Best Supportive Care Patients

Distribution	Adjustment factor (95% CI)	HR
Lognormal	–1.12 (–1.295; –0.955) or (–1.29; –0.959) when uncertainty around median PFS for BSC was not considered in the calculation of 95% CI for the comparison factor	TR=0.33*
Weibull	–1.25 (–1.418; –1.1079) or (–1.414; –1.084) when uncertainty around median PFS for BSC was not considered in the calculation of 95% CI for the comparison factor	HR=4.1 for BSC versus axitinib

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TR, time ratio.

**The lognormal distribution is not a proportional hazard model and, therefore, the HRs cannot be provided in this case. A HR cannot be calculated when a lognormal distribution is assumed; however, the comparison measure δ derived from a lognormal model can be expressed as the ratio of mean (progression-free or overall) survival times, TR, of comparator versus axitinib and calculated as TR=exp(δ).*

Table A2: Adjustment Factors for Overall Survival for Axitinib-like Patients – RECORD-1 Intention-to-Treat Best Supportive Care

Distribution	Adjustment factor (95% CI)	HR
Lognormal	–0.59 (–2.01; 0.82) or (–0.76; –0.43) when uncertainty around median OS for BSC was not considered in the calculation of 95% CI for the comparison factor	TR=0.55
Weibull	–0.68 (–2.10; 0.73) or (–0.85; –0.51) when uncertainty around median OS for BSC was not considered in the calculation of 95% CI for the comparison factor	HR=2.46 for BSC versus axitinib

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival; TR, time ratio.

The large difference in the CIs, with and without the uncertainty, around the median OS for BSC was due to the wide 95% CI for the acceleration factor, ψ, from the RPSFT analysis (0.5; 8.5).